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# Clinical Implications of Midventricular Obstruction in Patients With Hypertrophic Cardiomyopathy

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**Objectives** We investigated the prevalence, clinical characteristics, and prognosis of hypertrophic cardiomyopathy (HCM) patients with midventricular obstruction (MVO).

**Background** Previous descriptions of patients with MVO have been confined to case reports or small patient series, and this subgroup of HCM patients has therefore remained underrecognized.

**Methods** The study population included 490 HCM patients. Left ventricular MVO was diagnosed when the peak midcavitary gradient was estimated to be ≥30 mm Hg.

**Results** MVO was identified in 46 patients (9.4%). Patients with MVO were more likely to be symptomatic than those without. MVO was found to be an independent determinant of HCM-related death in multivariate models (hazard ratio [HR]: 2.23, $p = 0.016$), and this trend was especially pronounced for the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 3.19, $p < 0.001$). Apical aneurysm formation was identified in 28.3% of patients with MVO and strongly predicted HCM-related death (HR: 3.47, $p = 0.008$) and the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 5.08, $p < 0.001$). In addition, MVO without apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 2.43, $p = 0.045$).

**Conclusions** This analysis identified MVO as an independent predictor of adverse outcomes, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. Our results suggest that longer periods of exposure to MVO might lead to unfavorable consequences. They also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. (J Am Coll Cardiol 2011;57:2346–55)


Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by marked variability in morphological expression and natural history (1). Left ventricular intracavitary obstruction is an important pathophysiological component of HCM and classically occurs at the subaortic level, mainly due to systolic anterior motion (SAM) of the anterior mitral valve leaflet (1). This subaortic obstruction, called left ventricular outflow tract obstruction (OTO), occurs at rest in approximately 25% of patients with HCM and is an independent predictor of adverse clinical consequences (2,3). In a minority of HCM patients, however, the impedance to flow occurs at the midcavitary level, unrelated to SAM, and is predominantly caused by marked septal hypertrophy coming in contact with a hypercontractile left ventricular free wall, often with the interposition of the hypertrophied papillary muscle (4). Previous descriptions of these patients with midventricular obstruction (MVO) have been confined to case reports or small patient series because of the relative rarity and unique pathophysiology of the condition (5–13). Consequently, this subgroup of patients with HCM has remained underappreciated, and the clinical profiles of patients with MVO are largely undefined. This study was therefore undertaken to investigate the prevalence, clinical characteristics, and long-term prognosis of HCM patients with MVO.

## Methods

**Patients.** The study population included 490 patients with clinically diagnosed HCM who were enrolled and evaluated from 1980 to 2005 at Tokyo Women's Medical University Hospital, Tokyo, Japan. The initial evaluation was the first clinical assessment during which an echocardiogram diagnostic of HCM was obtained, and the most recent evaluation was

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performed in the clinic or by telephone interview. The study was performed according to the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee.

**HCM.** The diagnosis of HCM was based on the identification by 2-dimensional echocardiography of a hypertrophied, nondilated left ventricle in the absence of any other cardiac or systemic disease capable of producing a similar degree of hypertrophy (1).

**OTO and MVO.** Left ventricular OTO, caused by SAM of the anterior mitral valve leaflet, was considered to be present when the estimated peak instantaneous gradient was ≥30 mm Hg (3,14). Left ventricular MVO was diagnosed when both of the following criteria were satisfied: 1) the peak instantaneous midventricular gradient was estimated to be ≥30 mm Hg; and 2) midventricular obliteration was caused by marked septal hypertrophy resulting in contact with a hypercontractile left ventricular free wall rather than by SAM of the anterior mitral valve leaflet (6). Patients with both OTO (SAM) and MVO were excluded from the MVO group and included in the OTO group (6). This accounted for 6 of the 110 OTO patients (5.5%) in the current study.

**Apical hypertrophy and aneurysm.** The diagnostic criteria for apical hypertrophy included asymmetrical left ventricular hypertrophy, confined predominantly to the left ventricular apex, with an apical wall thickness ≥15 mm (15). A left ventricular apical aneurysm was defined as a discrete, thin-walled dyskinetic or akinetic segment of the most distal portion of the chamber with a relatively wide communication to the left ventricular cavity (16).

**Arrhythmias.** Documentation of atrial fibrillation was based on electrocardiographic recordings obtained either after acute onset of symptoms or fortuitously during routine medical examinations in asymptomatic patients. Ambulatory electrocardiograms covering at least a 24-h period were reviewed in all patients for the occurrence of nonsustained ventricular tachycardia, defined as a minimum of 3 consecutive ventricular beats with a rate of ≥120 beats/min (1).

**Mode of death.** Three modes of HCM-related death were defined for the purposes of survival analysis (1): 1) a combined endpoint of sudden death and potentially lethal arrhythmic events, in which unexpected death occurred in the absence of or <1 h from symptom onset in patients who had previously experienced a relatively stable or uneventful course, including resuscitated cardiac arrest and appropriate implantable defibrillator interventions; 2) heart failure–related death in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to end-stage phase; and 3) stroke-related death, which occurred in patients who died as a result of ischemic stroke.

**Echocardiography.** Echocardiographic studies were performed using commercially available ultrasound equipment. Complete M-mode, 2-dimensional, and Doppler studies were performed with the patient in the left lateral decubitus or supine position, using standard parasternal, apical, and subcostal approaches. Color Doppler imaging and pulse-wave Doppler echocardiography were used to localize the site of obstruction. Peak left ventricular intracavitary gradient was quantified using continuous-wave Doppler echocardiography under resting conditions. MVO was defined by systolic apposition of the mid-left ventricular walls, and often the papillary muscles, with abnormally high velocities persisting through late systole and often with early diastolic paradoxical jet flow (13). Contrast-enhanced echocardiography was performed by manual intravenous injection of 300 mg/ml galactose-palmitic acid (Levovist, Schering, Berlin, Germany) at a rate of 5 ml/5 s.

**Abbreviations and Acronyms**

CI = confidence interval
CMR = cardiovascular magnetic resonance
HCM = hypertrophic cardiomyopathy
HR = hazard ratio
MVO = midventricular obstruction
OTO = outflow tract obstruction
SAM = systolic anterior motion

**Cardiovascular magnetic resonance (CMR) imaging.** Studies were performed using a Magnetom Vision 1.5-T whole-body imaging system (Siemens Medical Systems, Erlangen, Germany [used from 2001 to July 2003]), or a Gyroscan Intera (Philips Medical Systems, Best, the Netherlands [used from July 2003 to 2005]). Breath-hold electrocardiography-gated cine steady-state free precession images were acquired in 7 to 10 short-axis slices and standard 2- and 4-chamber long-axis orientations. A delayed enhancement protocol was used 10 min after intravenous administration of 0.10 to 0.15 mmol/kg gadolinium-diethylenetriaminepentaacetic acid (Magnevist, Schering) with a breath-held segmented inversion-recovery sequence (inversion time, 230 to 300 ms, adjusted by a look-locker sequence) acquired in the same views as the cine images.

**Statistical analysis.** Analyses were performed using SAS system software, version 9.1 (SAS Institute, Cary, North Carolina). Data were presented as mean ± SD and frequencies. Student *t* tests were used to compare values between the 2 groups for continuous variables, and Mann-Whitney *U* tests were used for ordinal variables. Normality of distribution was assessed using the Kolmogorov-Smirnov test, and equality of variances was checked using the F statistic. A chi-square or Fisher exact test (when an expected value was <5) was used to compare nominally scaled variables. Event-free curves were estimated using the Kaplan-Meier method, and differences between curves were assessed by log-rank tests. Univariate and multivariate Cox proportional hazards models were applied to evaluate the influence of MVO and MVO with or without apical aneurysm on HCM-related death and the combined endpoint of sudden death and potentially lethal arrhythmic events. The proportional hazards assumption was confirmed by the log (−log survival function). The influences of profile, interaction, and collinearity in the models were examined using

regression diagnostic analysis. A 2-tailed p value <0.05 was considered to indicate a statistically significant difference.

## Results

**Prevalence and baseline characteristics.** MVO was identified in 46 of 490 HCM patients (9.4%). The baseline demographic and clinical characteristics of the HCM patients with and without MVO are shown in Table 1. The mean age at diagnosis of the 46 patients with MVO was 53.2 ± 14.7 years (range 19 to 77 years). The New York Heart Association functional class at diagnosis in patients with MVO was significantly higher than that in those without MVO. However, there were no statistically significant differences with respect to sex, age, family history of sudden death, maximal left ventricular wall thickness, or arrhythmias between patients with and without MVO.

**Comparison with OTO and treatments.** OTO was identified in 110 of 490 HCM patients (22.4%). The demographic, clinical, and therapeutic characteristics of the 46 patients with MVO and the 110 patients with OTO are shown in Table 2. There was a higher proportion of male patients with MVO than with OTO, and patients with MVO had a lower left ventricular intracavitary gradient at diagnosis. Of the 46 patients with MVO, 43 (93.5%) were treated with negative inotropic agents, such as beta-blockers, calcium-channel blockers, and/or class I antiarrhythmic drugs (mainly disopyramide). Three patients (6.5%) underwent dual-chamber pacing therapy, and only 1 patient (2.2%) underwent surgery to reduce the gradient caused by MVO.

**Outcomes.** Six of the 46 patients with MVO (13.0%) experienced episodes of progressive heart failure with an increase to ≥3 New York Heart Association functional class, and 5 patients (10.9%) had nonfatal thromboembolic strokes over the mean follow-up period of 10.4 ± 8.2 years. Eleven patients (23.9%) experienced HCM-related death including 2 patients with sudden death, 7 patients with successfully resuscitated cardiac arrest (with documented ventricular fibrillation [n = 5] and with documented ventricular tachycardia with pulseless collapse [n = 2]), and 2 patients with appropriate implantable defibrillator interventions. In univariate analysis, patients with MVO had a significantly greater likelihood of HCM-related death than patients without MVO (log-rank p = 0.017) (Fig. 1A). The probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was also significantly higher than that among patients without MVO (log-rank p < 0.001) (Fig. 1B). The frequency of HCM-related death in patients with MVO was similar to that in patients with OTO (log-rank p = 0.451) (Fig. 2A). Conversely, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was significantly higher than that among patients with OTO (log-rank p = 0.038) (Fig. 2B). In multivariate modeling, entering MVO and established major primary prevention risk factors for sudden death (family history of sudden death, maximum left ventricular wall thickness ≥30 mm, nonsustained ventricular tachycardia, and unexplained syncope) (1,17), MVO was identified as an independent determinant of outcome, including the risk of HCM-related death (adjusted hazard ratio [HR]: 2.23, 95% confidence interval [CI]: 1.16 to 4.29; p = 0.016) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 3.19, 95% CI: 1.62 to 6.29; p < 0.001) (Table 3). Exercise tests were not performed in all HCM patients, and abnormal exercise blood pressure was therefore excluded from the analysis. The sensitivities of MVO for HCM-

**Table 1** Baseline Characteristics of HCM Patients With and Without MVO

| | Patients With MVO (n = 46) | Patients Without MVO (n = 444) | p Value |
|---|---|---|---|
| Male | 28 (60.9) | 288 (64.9) | 0.590 |
| Age at diagnosis, yrs | 53.2 ± 14.7 | 50.4 ± 14.9 | 0.232 |
| Family history of sudden death | 6 (13.0) | 55 (12.4) | 0.898 |
| Maximal left ventricular wall thickness, mm | 19.1 ± 4.3 | 19.7 ± 4.2 | 0.345 |
| Apical aneurysm formation | 13 (28.3) | 8 (1.8) | <0.001 |
| Nonsustained ventricular tachycardia | 14 (30.4) | 182 (41.0) | 0.164 |
| Atrial fibrillation | 11 (23.9) | 140 (31.5) | 0.287 |
| Unexplained syncope | 12 (26.1) | 80 (18.0) | 0.182 |
| NYHA functional class at diagnosis | | | 0.004 |
| I | 13 (28.3) | 247 (55.6) | |
| II | 31 (67.4) | 159 (35.8) | |
| III | 2 (4.3) | 35 (7.9) | |
| IV | 0 (0.0) | 3 (0.7) | |
| Progressive heart failure | 6 (13.0) | 53 (11.9) | 0.826 |
| Stroke | 5 (10.9) | 56 (12.6) | 0.733 |
| Follow-up duration, yrs | 10.4 ± 8.2 | 11.7 ± 7.3 | 0.266 |

Values are n (%) or mean ± SD.
HCM = hypertrophic cardiomyopathy; MVO = midventricular obstruction; NYHA = New York Heart Association.

**Table 2** Demographic, Clinical, and Therapeutic Characteristics of HCM Patients With MVO and With OTO

| | Patients With MVO (n = 46) | Patients With OTO (n = 110) | p Value |
|---|---|---|---|
| Male | 28 (60.9) | 48 (43.6) | 0.050 |
| Age at diagnosis, yrs | 53.2 ± 14.7 | 55.1 ± 15.7 | 0.483 |
| Family history of sudden death | 6 (13.0) | 11 (10.0) | 0.578 |
| Maximum left ventricular wall thickness, mm | 19.1 ± 4.3 | 20.0 ± 4.9 | 0.239 |
| Apical aneurysm formation | 13 (28.3) | 2 (1.8) | <0.001 |
| Nonsustained ventricular tachycardia | 14 (30.4) | 36 (32.7) | 0.780 |
| Atrial fibrillation | 11 (23.9) | 36 (32.7) | 0.274 |
| Unexplained syncope | 12 (26.1) | 22 (20.0) | 0.401 |
| NYHA functional class at diagnosis | | | 0.927 |
| I | 13 (28.3) | 39 (35.5) | |
| II | 31 (67.4) | 57 (51.8) | |
| III | 2 (4.3) | 13 (11.8) | |
| IV | 0 (0.0) | 1 (0.9) | |
| Progressive heart failure | 6 (13.0) | 14 (12.7) | 0.957 |
| Stroke | 5 (10.9) | 13 (11.8) | 0.866 |
| Pressure gradient at diagnosis, mm Hg | 45.9 ± 14.7 | 81.0 ± 30.1 | <0.001 |
| Treatments | | | |
| Beta-blockers | 35 (76.1) | 92 (83.6) | 0.269 |
| Calcium-channel blockers | 14 (30.4) | 26 (23.6) | 0.375 |
| Class I antiarrhythmic drugs | 16 (34.8) | 69 (62.7) | 0.001 |
| All interventions combined | 4 (8.7) | 36 (32.7) | 0.002 |
| Warfarin | 13 (28.3) | 35 (31.8) | 0.661 |
| Follow-up duration, yrs | 10.4 ± 8.2 | 10.0 ± 6.7 | 0.761 |

Values are n (%) or mean ± SD.
OTO = outflow tract obstruction; other abbreviations as in Table 1.

related death/combined endpoint of sudden death and potentially lethal arrhythmic events were 17.2%/22.9%, respectively, and the corresponding specificities were 91.8%/92.1%, respectively.

**Apical hypertrophy and apical aneurysm formation.** Left ventricular apical hypertrophy was identified in 16 of the 46 patients with MVO (34.8%). All the 16 patients exhibited mid-left ventricular hypertrophy, and none had hypertrophy

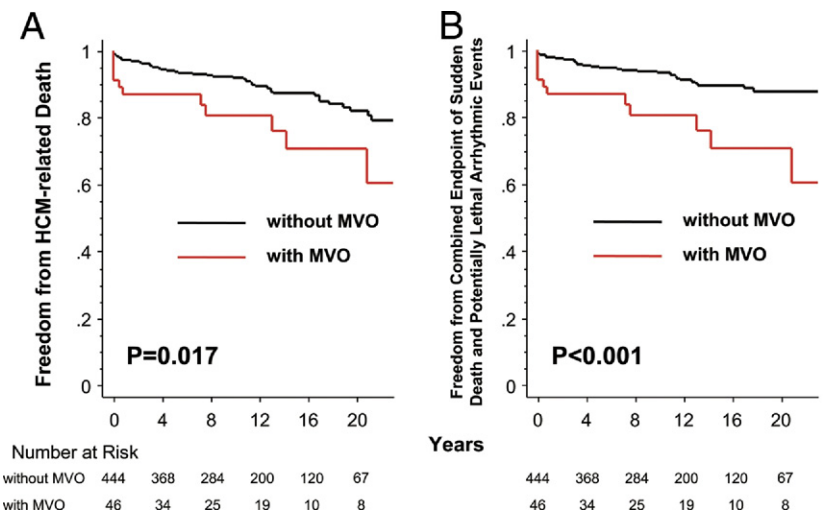


**Figure 1** Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 444 Patients Without MVO

Patients with midventricular obstruction (MVO) had a significantly greater likelihood of hypertrophic cardiomyopathy (HCM)–related death **(A)** and the combined endpoint of sudden death and potentially lethal arrhythmic events **(B)** than patients without MVO.

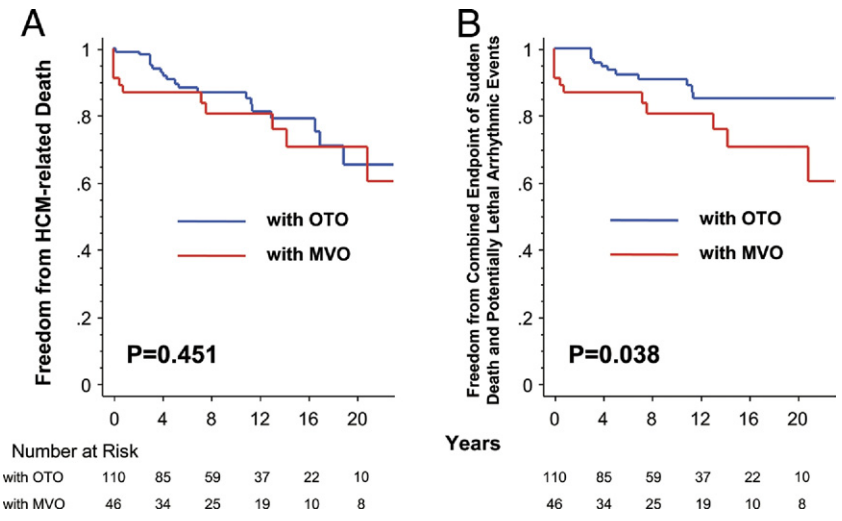


**Figure 2** **Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 110 Patients With OTO**

There was no statistically significant difference in HCM-related death rate between patients with MVO and patients with outflow tract obstruction (OTO) **(A)**. However, patients with MVO had a significantly greater likelihood of the combined endpoint of sudden death and potentially lethal arrhythmic events than patients with OTO **(B)**. Abbreviations as in Figure 1.

confined only to the left ventricular apex below the papillary muscle level. Left ventricular apical aneurysm was identified in 13 of the 46 patients with MVO (28.3%). Coronary artery disease was excluded as a cause of apical aneurysm formation by the absence of significant coronary arterial narrowing (>50% stenosis) in the left anterior descending artery using conventional coronary angiography (n = 10) and no history of chest pain, coronary risk factors, or acute coronary syndrome (n = 3, all younger than 60 years of age). An apical aneurysm was confirmed by CMR in 8 of the 13 patients. All the 8 patients exhibited late gadolinium enhancement in the apical aneurysmal wall itself, with extension into the hypertrophic region of the left ventricle. An apical aneurysm was confirmed by contrast-enhanced echocardiography in the remaining 5 patients who did not undergo CMR. Development of an apical aneurysm from MVO was observed in 6 of 13 aneurysm patients during the follow-up period (Figs. 3 and 4). In the remaining 7 patients, an apical aneurysm was observed at the initial evaluation. In 2 of 6 patients in whom an apical aneurysm developed from MVO, CMR was performed both before and after aneurysm formation, and these 2 patients already exhibited late gadolinium enhancement in the apex before detection of the apical aneurysm formation (Fig. 3C). The baseline characteristics of the HCM patients with MVO, according to the presence or absence of an apical aneurysm, are shown in Table 4. The frequency of nonsustained ventricular tachycardia in patients with an aneurysm was significantly higher than in those without an aneurysm. In contrast to the situation in patients with MVO, only 2 of the 110 patients with OTO (1.8%), and only 8 of the 444 patients without MVO (1.8%) were complicated by an apical aneurysm (Tables 1 and 2).

**Relationship of apical aneurysm formation to outcomes.** When patients with MVO were divided into those with (n = 13) and those without (n = 33) an apical aneurysm, 5 of 13 MVO patients with an apical aneurysm (38.5%) experienced HCM-related death, including sudden death (n = 1), resuscitated cardiac arrest (n = 3), and appropriate implantable defibrillator interventions (n = 1). One of the 5 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. Six of the 33 MVO patients without an apical aneurysm (18.2%) experienced HCM-related death. Two of the 6 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. In multivariate models including MVO with or without an apical aneurysm and established major primary prevention risk factors for sudden death, apical aneurysm formation in patients with MVO strongly predicted HCM-related death (adjusted HR: 3.47, 95% CI: 1.38 to 8.73; p = 0.008) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 5.08, 95% CI: 1.97 to 13.05; p < 0.001). MVO without an apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 2.43, 95% CI: 1.02 to 5.80; p = 0.045), but was not identified as an independent determinant of HCM-related death overall (adjusted HR: 1.72, 95% CI: 0.73 to 4.02; p = 0.213).

## Discussion

In the current single-center patient cohort, MVO was confirmed in 9.4% of patients with HCM. Although no

**Table 3** Predictors of HCM-Related Adverse Events in Univariate and Multivariate Analysis of MVO and Established Major Primary Prevention Risk Factors for Sudden Death

| Variables | No. of Patients | HCM-Related Death | | | | Combined Endpoint of Sudden Death and Potentially Lethal Arrhythmic Events | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. (%) of Events | Crude Hazard Ratio (95% CI) | p Value | Adjusted Hazard Ratio (95% CI) | p Value | No. (%) of Events | Crude Hazard Ratio (95% CI) | p Value | Adjusted Hazard Ratio (95% CI) | p Value |
| Family history of sudden death | | | | | | | | | | | |
| Absent | 429 | 51 (11.9) | 1.00 | | 1.00 | | 38 (8.9) | 1.00 | | 1.00 | |
| Present | 61 | 13 (21.3) | 1.68 (0.91–3.09) | 0.096 | 1.35 (0.73–2.51) | 0.338 | 10 (16.4) | 1.82 (0.90–3.65) | 0.094 | 1.41 (0.69–2.85) | 0.344 |
| Left ventricular wall thickness ≥30 mm | | | | | | | | | | | |
| Absent | 475 | 59 (12.4) | 1.00 | | 1.00 | | 43 (9.1) | 1.00 | | 1.00 | |
| Present | 15 | 5 (33.3) | 2.89 (1.15–7.25) | 0.024 | 3.26 (1.29–8.25) | 0.012 | 5 (33.3) | 3.56 (1.41–9.02) | 0.007 | 4.35 (1.69–11.19) | 0.002 |
| Nonsustained ventricular tachycardia | | | | | | | | | | | |
| Absent | 294 | 30 (10.2) | 1.00 | | 1.00 | | 21 (7.1) | 1.00 | | 1.00 | |
| Present | 196 | 34 (17.3) | 1.54 (0.94–2.53) | 0.084 | 1.37 (0.83–2.25) | 0.218 | 27 (13.8) | 1.80 (1.02–3.19) | 0.043 | 1.54 (0.86–2.76) | 0.146 |
| Unexplained syncope | | | | | | | | | | | |
| Absent | 398 | 37 (9.3) | 1.00 | | 1.00 | | 24 (6.0) | 1.00 | | 1.00 | |
| Present | 92 | 27 (29.3) | 3.40 (2.07–5.58) | <0.001 | 3.23 (1.94–5.38) | <0.001 | 24 (26.1) | 4.66 (2.64–8.20) | <0.001 | 4.32 (2.41–7.78) | <0.001 |
| MVO | | | | | | | | | | | |
| Absent | 444 | 53 (11.9) | 1.00 | | 1.00 | | 37 (8.3) | 1.00 | | 1.00 | |
| Present | 46 | 11 (23.9) | 2.17 (1.13–4.15) | 0.020 | 2.23 (1.16–4.29) | 0.016 | 11 (23.9) | 3.16 (1.61–6.20) | <0.001 | 3.19 (1.62–6.29) | <0.001 |

CI = confidence interval; other abbreviations as in Table 1.

extensive clinical studies have been designed to determine the true prevalence of MVO in patients with HCM, MVO with an akinetic apical chamber has been considered to be a rare form of HCM, occurring in 1% of cases in the non-Asian population (5). According to a report from the United States, however, MVO was found in 8 of 62 patients (12.9%) with a diagnosis of HCM (18). In addition, MVO was present in 10.9% of patients with HCM in a 5-year study performed at an echocardiography laboratory in Italy (19). Furthermore, diastolic paradoxical jet flow across the obliterated left ventricular apex toward the base, suggestive of MVO and a discrete apical chamber, was present in 20 of 198 patients (10.1%) with HCM in a previous study (20). These variations in prevalence could be the result of racial/ethnic differences, selection bias, underrecognition, misdiagnosis, or differences in the definitions of MVO. Despite being based on a highly selected population of patients with HCM from a single large tertiary referral center in Japan, the results of the current study have revealed novel epidemiological information about MVO in a relatively large HCM patient cohort.

A left ventricular apical aneurysm was identified in approximately one-fourth of HCM patients with MVO in the current study. Numerous previous case reports and studies have indicated that MVO is associated with an apical aneurysm in patients with HCM (5,7,8,16). Maron et al. (16) hypothesized that a left ventricular apical aneurysm and the associated regional myocardial scarring developed secondarily to increased left ventricular wall stress as a result of MVO and elevated intracavitary systolic pressures. Increased wall stress imposes an increased pressure load on the apical myocardium, increasing its oxygen demand, and impairs coronary flow through extravascular compression of the coronary artery, leading to chronic myocardial ischemia and aneurysm formation. The results of the current study, as well as those of previous studies, suggest the existence of a close overlap between MVO and an apical aneurysm in patients with HCM.

The presence of MVO was identified as an independent determinant of unfavorable outcomes in our analysis. In addition, apical aneurysm formation in patients with MVO more strongly predicted HCM-related adverse events. A recent study demonstrated a largely unfavorable clinical course in 28 HCM patients with an apical aneurysm. Twelve of the 28 patients (42.9%) either died of their disease or survived with severe adverse HCM-related events (16). Similarly, 5 of 13 patients (38.5%) with MVO and an apical aneurysm experienced HCM-related death in the present study. These results suggest that the higher mortality observed in patients with MVO might be due partly to aneurysm formation, which may develop secondarily to increased left ventricular wall stress as a result of MVO. Furthermore, the scarred rim of the aneurysm and the associated extensive areas of myocardial fibrosis have been regarded as arrhythmogenic substrates for the generation of malignant ventricular tachyarrhythmias (21,22). It is there-

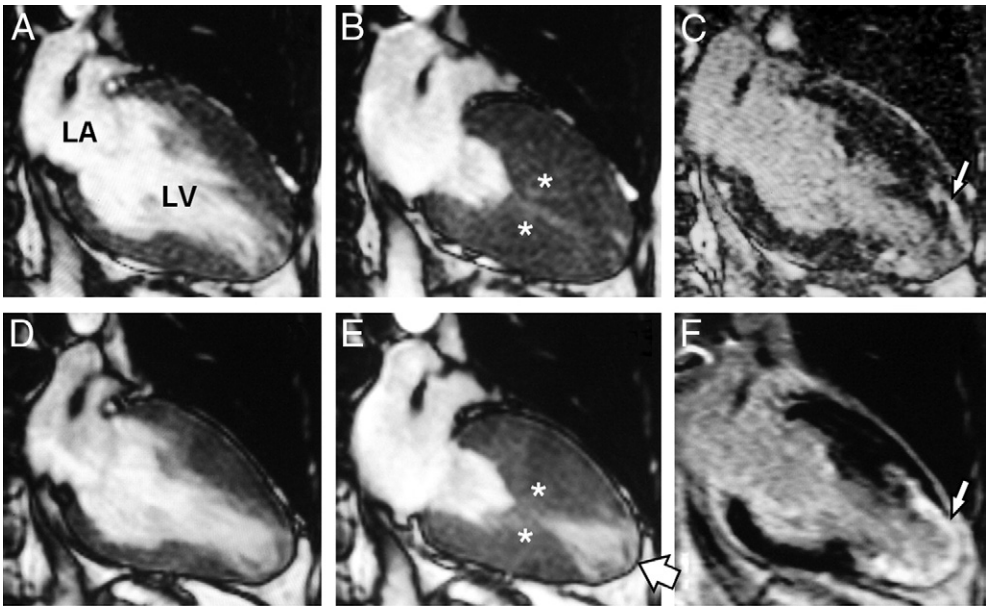


**Figure 3** **CMR Images From an HCM Patient in Whom an Apical Aneurysm Developed From MVO**

Left ventricular long-axis 2-chamber cardiovascular magnetic resonance (CMR) cine images in end-diastole **(A)** and end-systole **(B)** from a 67-year-old HCM patient with MVO **(*)**. Identical imaging view in the same patient with gadolinium-diethylenetriaminepentaacetic acid already showing late gadolinium enhancement in the apex **(thin arrow, C)**. After 4 years, 2-chamber long-axis CMR images in end-diastole **(D)** and end-systole **(E)** demonstrating apical aneurysm formation **(thick arrow)**, which was associated with regional transmural late gadolinium enhancement of the aneurysmal wall **(thin arrow, F)**. LA = left atrium; LV = left ventricle; other abbreviations as in Figure 1.

fore not surprising that the majority of reported HCM-related events in patients with MVO and an apical aneurysm may be caused by ventricular arrhythmias (7,8). These observations suggest that the treatment of patients with MVO already complicated by an apical aneurysm should be modified to include primary prevention of sudden death with the use of an implanted defibrillator (16). In addition, MVO without an apical aneurysm was also associated with the risk of the combined endpoint of sudden death and potentially lethal arrhythmic events in this study. Furthermore, 2 MVO patients without an apical aneurysm and with no additional established major primary prevention risk factors for sudden death experienced adverse events. Additional clinical studies are needed to clarify whether the presence of MVO alone justifies the prophylactic use of an implantable defibrillator.

In this analysis, we also compared patients with MVO and those with OTO. Intriguingly, we found that the probability of HCM-related death in patients with MVO was similar to that in patients with OTO. Furthermore, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events in patients with MVO was higher than that in patients with OTO. This suggests that MVO could be as predictive of unfavorable outcomes as OTO because of increased wall stress, apical aneurysm formation, apical myocardial infarction, and myocardial scarring (16,21,22). Timely recognition of MVO might thus affect clinical practice decisions by prompting consideration of gradient and wall stress relief with negative inotropic agents and/or therapeutic interventions. Numerous previous studies have demonstrated a reduction in intracavitary pressure gradients in HCM patients with MVO after dual-chamber pacing and myectomy (9–13). Successful surgical septal myectomy in OTO patients can completely abolish the gradients, leading to marked improvement of symptoms and outcomes (23). Surgical relief of MVO by extensive mid-left ventricular resection may thus similarly reduce HCM-related adverse events. However, patients with MVO had a lower left ventricular intracavitary gradient than those with OTO in our study cohort. In addition, MVO patients with an apical aneurysm had slightly lower midcavitary gradient than those without. This may be due partly to apical systolic dysfunction (hypokinesia, akinesia, or dyskinesia) and the midsystolic decrease in flow that can occur in patients with MVO (13,24). Lower gradients might lead to underestimation of the prognostic significance of MVO, resulting in inadequate medication and/or therapeutic interventions for the gradients of MVO. In comparison with OTO, MVO patients in this study used class I antiarrhythmic drugs less and had fewer invasive procedures to reduce the gradient of MVO, despite poor outcomes in the MVO patient group. Further studies are required to evaluate the actual severity of MVO and to determine the most appropriate treatment strategies for gradient reduction in patients with MVO.

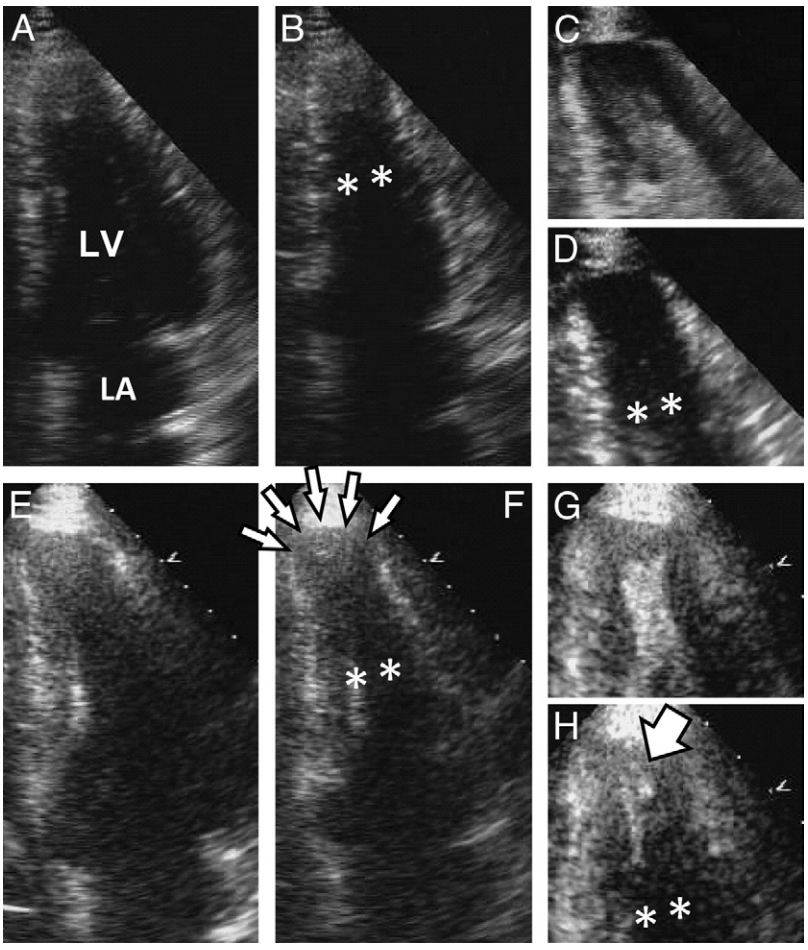


**Figure 4** **Echocardiographic Images of an HCM Patient in Whom an Apical Aneurysm Developed From MVO**

Left ventricular apical 4-chamber views in end-diastole **(A)** and end-systole **(B)** in a 60-year-old HCM patient with MVO **(*)**. Contrast-enhanced 4-chamber views in end-diastole **(C)** and end-systole **(D)** showing no systolic pooling of contrast agent. Four-chamber views in end-diastole **(E)** and end-systole **(F)** in the same patient with MVO **(*)** after 4 years demonstrating apical aneurysm formation **(thin arrows)**. Contrast-enhanced 4-chamber views in end-diastole **(G)** and end-systole **(H)** showing apical systolic pooling of contrast agent **(thick arrow)**. Abbreviations as in Figures 1 and 3.

**Study limitations.** The present study was based on the retrospective enrollment of individual patients with HCM, which is an unavoidable limitation shared by virtually all large-scale clinical studies on HCM. This study was evaluated in a single tertiary referral center in Japan and was therefore subject to selection bias by including a highly selected population of patients with HCM. In addition, some HCM patients were taking medication before their referral to our center, and the initial echocardiographic studies in some patients were thus performed while they were taking medication. Our results were thus likely to underestimate the prevalence and severity of MVO and OTO in this HCM patient cohort. The detection of apical hypertrophy and aneurysms in this study was based partly on transthoracic echocardiography, which has proven to be less reliable for detecting apical hypertrophy and aneurysms compared with the higher spatial resolution and detection capability of CMR imaging. In addition to CMR, contrast-enhanced echocardiography allows better delineation of the apical endocardium when apical acoustic windows are difficult to obtain (25). However, CMR and contrast-enhanced echocardiography were not performed in all MVO cases in this study, and our data were therefore likely to underestimate the true prevalence of apical hypertrophy and aneurysms in this cohort of patients with MVO.

## Conclusions

In this HCM patient cohort, MVO was identified as an independent determinant of HCM-related death, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. In addition, apical aneurysm formation in patients with MVO was more

**Table 4** Baseline Characteristics of HCM Patients With MVO According to the Presence or Absence of an Apical Aneurysm

| | Patients With an Aneurysm (n = 13) | Patients Without an Aneurysm (n = 33) | p Value |
|---|---|---|---|
| Male | 10 (76.9) | 18 (54.5) | 0.161 |
| Age at diagnosis, yrs | 50.5 ± 12.5 | 54.2 ± 15.5 | 0.447 |
| Family history of sudden death | 2 (15.4) | 4 (12.1) | >0.999 |
| Maximum left ventricular wall thickness, mm | 19.1 ± 4.1 | 19.1 ± 4.5 | 0.991 |
| Nonsustained ventricular tachycardia | 7 (53.8) | 7 (21.2) | 0.041 |
| Atrial fibrillation | 3 (23.1) | 8 (24.2) | >0.999 |
| Unexplained syncope | 5 (38.5) | 7 (21.2) | 0.276 |
| NYHA functional class at diagnosis | | | 0.513 |
| I | 3 (23.1) | 10 (30.3) | |
| II | 9 (69.2) | 22 (66.7) | |
| III | 1 (7.7) | 1 (3.0) | |
| IV | 0 (0.0) | 0 (0.0) | |
| Progressive heart failure | 2 (15.4) | 4 (12.1) | >0.999 |
| Stroke | 1 (7.7) | 4 (12.1) | >0.999 |
| Pressure gradient at diagnosis, mm Hg | 41.9 ± 12.1 | 47.5 ± 15.5 | 0.252 |
| Treatments | | | |
| Beta-blockers | 11 (84.6) | 24 (72.7) | 0.473 |
| Calcium-channel blockers | 2 (15.4) | 12 (36.4) | 0.286 |
| Class I antiarrhythmic drugs | 4 (30.8) | 12 (36.4) | >0.999 |
| All interventions combined | 2 (15.4) | 2 (6.1) | 0.565 |
| Warfarin | 6 (46.2) | 7 (21.2) | 0.145 |
| Follow-up duration, yrs | 11.2 ± 10.3 | 10.1 ± 7.4 | 0.682 |

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

strongly associated with adverse outcomes. Our results suggest that longer periods of exposure to MVO and increased left ventricular wall stress might lead to apical aneurysm formation and clinically unfavorable consequences. The results also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. Timely recognition of MVO might thus prompt changes in clinical practice to allow for gradient relief and prophylactic defibrillator implantation and could also guide the challenge of improving the prognosis for HCM patients with MVO. Further studies are required to determine the most appropriate treatment strategies for patients with MVO.

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## REFERENCES

1. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.
2. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol 2005;45:1076–80.
3. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295–303.
4. Falicov RE, Resnekov L. Mid ventricular obstruction in hypertrophic obstructive cardiomyopathy. New diagnostic and therapeutic challenge. Br Heart J 1977;39:701–5.
5. Duncan K, Shah A, Chaudhry F, Sherrid MV. Hypertrophic cardiomyopathy with massive midventricular hypertrophy, midventricular obstruction and an akinetic apical chamber. Anadolu Kardiyol Derg 2006;6:279–82.
6. Hamada M, Shigematsu Y, Inaba S, et al. Antiarrhythmic drug cibenzoline attenuates left ventricular pressure gradient and improves transmitral Doppler flow pattern in patients with hypertrophic obstructive cardiomyopathy caused by midventricular obstruction. Circ J 2005;69:940–5.
7. Sanghvi NK, Tracy CM. Sustained ventricular tachycardia in apical hypertrophic cardiomyopathy, midcavitary obstruction, and apical aneurysm. Pacing Clin Electrophysiol 2007;30:799–803.
8. Tse HF, Ho HH. Sudden cardiac death caused by hypertrophic cardiomyopathy associated with midventricular obstruction and apical aneurysm. Heart 2003;89:178.

9. Schulte HD, Bircks W, Korfer R, Kuhn H. Surgical aspects of typical subaortic and atypical midventricular hypertrophic obstructive cardiomyopathy (HOCM). Thorac Cardiovasc Surg 1981;29:375–80.
10. Bircks W, Schulte HD. Surgical treatment of hypertrophic obstructive cardiomyopathy with special reference to complications and to atypical hypertrophic obstructive cardiomyopathy. Eur Heart J 1983; 4 Suppl F:187–90.
11. Begley D, Mohiddin S, Fananapazir L. Dual chamber pacemaker therapy for mid-cavity obstructive hypertrophic cardiomyopathy. Pacing Clin Electrophysiol 2001;24:1639–44.
12. Cecchi F, Olivotto I, Nistri S, Antoniucci D, Yacoub MH. Midventricular obstruction and clinical decision-making in obstructive hypertrophic cardiomyopathy. Herz 2006;31:871–6.
13. Shah A, Duncan K, Winson G, Chaudhry FA, Sherrid MV. Severe symptoms in mid and apical hypertrophic cardiomyopathy. Echocardiography 2009;26:922–33.
14. Panza JA, Petrone RK, Fananapazir L, Maron BJ. Utility of continuous wave Doppler echocardiography in the noninvasive assessment of left ventricular outflow tract pressure gradient in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1992;19:91–9.
15. Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;39:638–45.
16. Maron MS, Finley JJ, Bos JM, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation 2008;118:1541–9.
17. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212–8.
18. Fighali S, Krajcer Z, Edelman S, Leachman RD. Progression of hypertrophic cardiomyopathy into a hypokinetic left ventricle: higher incidence in patients with midventricular obstruction. J Am Coll Cardiol 1987;9:288–94.
19. de Gregorio C. Left ventricular dynamic obstruction by atypical papillary muscle morphology: is this finding so unusual in clinical practice? J Am Soc Echocardiogr 2007;20:100–1.
20. Nakamura T, Matsubara K, Furukawa K, et al. Diastolic paradoxic jet flow in patients with hypertrophic cardiomyopathy: evidence of concealed apical asynergy with cavity obliteration. J Am Coll Cardiol 1992;19:516–24.
21. Adabag AS, Maron BJ, Appelbaum E, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol 2008;51:1369–74.
22. Kwon DH, Smedira NG, Rodriguez ER, et al. Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. J Am Coll Cardiol 2009;54:242–9.
23. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470–6.
24. Sherrid MV, Wever-Pinzon O, Shah A, Chaudhry FA. Reflections of inflections in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54:212–9.
25. Ward RP, Weinert L, Spencer KT, et al. Quantitative diagnosis of apical cardiomyopathy using contrast echocardiography. J Am Soc Echocardiogr 2002;15:316–22.

**Key Words:** epidemiology ■ hypertrophic cardiomyopathy ■ midventricular obstruction ■ prognosis.